



This is an electronic reprint of the original article. This reprint may differ from the original in pagination and typographic detail.

Desforges, Manon; Hadas, Itay; Mihov, Brian; Morin, Yan; Rochette Braün, Mathilde; Lioumis, Pantelis; Zomorrodi, Reza; Théoret, Hugo; Lepage, Martin; Daskalakis, Zafiris J.; Tremblay, Sara

Dose-response of intermittent theta burst stimulation of the prefrontal cortex : A TMS-EEG study

Published in: Clinical Neurophysiology

DOI: 10.1016/j.clinph.2021.12.018

Published: 01/04/2022

Document Version Publisher's PDF, also known as Version of record

Published under the following license: CC BY-NC-ND

*Please cite the original version:* Desforges, M., Hadas, I., Mihov, B., Morin, Y., Rochette Braün, M., Lioumis, P., Zomorrodi, R., Théoret, H., Lepage, M., Daskalakis, Z. J., & Tremblay, S. (2022). Dose-response of intermittent theta burst stimulation of the prefrontal cortex : A TMS-EEG study. *Clinical Neurophysiology*, *136*, 158-172. https://doi.org/10.1016/j.clinph.2021.12.018

This material is protected by copyright and other intellectual property rights, and duplication or sale of all or part of any of the repository collections is not permitted, except that material may be duplicated by you for your research use or educational purposes in electronic or print form. You must obtain permission for any other use. Electronic or print copies may not be offered, whether for sale or otherwise to anyone who is not an authorised user.

Clinical Neurophysiology 136 (2022) 158-172

Contents lists available at ScienceDirect

# Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

# Dose-response of intermittent theta burst stimulation of the prefrontal cortex: A TMS-EEG study



Manon Desforges <sup>a,b</sup>, Itay Hadas <sup>c</sup>, Brian Mihov <sup>d</sup>, Yan Morin <sup>a</sup>, Mathilde Rochette Braün <sup>e</sup>, Pantelis Lioumis <sup>f</sup>, Reza Zomorrodi <sup>g</sup>, Hugo Théoret <sup>a</sup>, Martin Lepage <sup>d,h</sup>, Zafiris J. Daskalakis <sup>c,g</sup>, Sara Tremblay <sup>b,i,j,\*</sup>

<sup>a</sup> Department of Psychology, University of Montreal, Montreal, Canada

<sup>b</sup> The Royal's Institute of Mental Health Research, affiliated with the University of Ottawa, Ottawa, Canada

<sup>c</sup> Department of Psychiatry, Faculty of Health, University of California San Diego, La Jolla, USA

<sup>d</sup> McGill University, Montreal, Canada

<sup>e</sup> Department of Psychology, Université du Québec à Montréal, Montreal, Canada

<sup>f</sup> Department of Neuroscience and Biomedical Engineering, Aalto University, Espoo, Finland

<sup>g</sup> Temerty Centre for Therapeutic Brain Intervention, Center for Addiction and Mental Health, Toronto, Canada

<sup>h</sup> Douglas Mental Health University Institute, Montreal, Canada

<sup>1</sup>Département de psychoéducation et psychologie, Université du Québec en Outaouais, Gatineau, Québec, Canada

<sup>j</sup> Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Canada

# ARTICLE INFO

Article history: Accepted 26 December 2021 Available online 20 January 2022

Keywords: rTMS iTBS Dorsolateral prefrontal cortex Neuroplasticity Healthy subjects TMS-EEG

# HIGHLIGHTS

- The effects of 600, 1200 and 1800 pulses of intermittent theta burst stimulation were compared in healthy volunteers.
- None of the three doses was superior in modulating prefrontal evoked activity and oscillatory activity.
- iTBS may act on dorsolateral prefrontal cortex activity via the modulation of excitation/inhibition balance.

# ABSTRACT

*Objective:* Using concurrent transcranial magnetic stimulation (TMS) and electroencephalography (TMS-EEG), this study aims to compare the effect of three intermittent theta-burst stimulation (iTBS) doses on cortical activity in the left dorsolateral prefrontal (DLPFC) cortex.

*Methods:* Fourteen neurotypical participants took part in the following three experimental conditions: 600, 1200 and 1800 pulses. TMS-EEG recordings were conducted on the left DLPFC pre/post iTBS, including single-pulse TMS and short- and long-interval intracortical inhibition (SICI, LICI). TMS-evoked potentials (TEP) and event-related spectral perturbation (ERSP) were quantified. Linear mixed models were used to assess the effect of iTBS on brain activity.

*Results:* The effects of iTBS on DLPFC activity did not significantly differ between the three doses. Specifically, regardless of dose, iTBS modulated the amplitude of most TEP components (P30, N45, P60, P200), reduced SICI and LICI ratios of P30 and P200, and decreased ERSP power of theta oscillations.

*Conclusions:* In neurotypical individuals, doubling or tripling the number of iTBS pulses does not result in stronger potentiation of prefrontal activity. However, all iTBS conditions induced significant modulations of DLPFC activity.

*Significance:* Replicating the study in clinical populations could help define optimal parameters for clinical applications.

© 2022 International Federation of Clinical Neurophysiology. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

\* Corresponding author at: The Royal's Institute of Mental Health Research, University of Ottawa, 1145 Carling Ave., Ottawa, Ont. K1Z 7K4, Canada. *E-mail address:* sara.tremblay@theroyal.ca (S. Tremblay).

# 1. Introduction

Theta burst stimulation (TBS) is based on protocols employed to induce plastic changes in animal brain slices (Capocchi et al., 1992; Staubli and Lynch, 1987). The excitatory form of TBS, i.e. intermit-

https://doi.org/10.1016/j.clinph.2021.12.018

1388-2457/© 2022 International Federation of Clinical Neurophysiology. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). tent TBS (iTBS), has been shown to increase cortical excitability in the primary motor cortex, thus potentially reflecting long-term potentiation mechanisms (Suppa et al., 2016). The standard iTBS protocol is defined as 2 s trains of TBS repeated every 10 s for a total of 600 pulses (Huang et al., 2005). However, a meta-analysis of studies that targeted the motor cortex (Chung et al., 2016) showed that non-standard iTBS doses are often used, including 150 pulses (Huang et al., 2010), 2 blocks of 600 pulses (Mastroeni et al., 2013), 1200 pulses (Gamboa et al., 2010; Hsu et al., 2011; Mastroeni et al., 2013; Nettekoven et al., 2014), and 1800 pulses (Nettekoven et al., 2014). Doses above the standard protocol are also increasingly used for stimulating the dorsolateral prefrontal cortex (DLPFC), the main therapeutic target for treating major depressive disorder (MDD) (Chistyakov et al., 2010). Although some studies employed the standard dose of 600 pulses (Blumberger et al., 2018; Cristancho et al., 2020), most clinical protocols set stimulation doses at 1200 pulses (Prasser et al., 2015), 2 blocks of 600 pulses (Plewnia et al., 2014; Zavorotnyy et al., 2020) or 1800 pulses (Chistyakov et al., 2010; Dhami et al., 2019; Li et al., 2014; Li et al., 2018). Furthermore, new accelerated and high dose iTBS protocols were recently developed (Caulfield, 2020), consisting of multiple sessions per day, ranging from 5 consecutive daily sessions of 1620 pulses (Baeken et al., 2017; Duprat et al., 2016) to 10 consecutive sessions of 1800 pulses (Williams et al., 2018).

The increased iTBS dose is generally based on the assumption that it will enhance its effect on brain activity, resulting in increased therapeutic effects. Yet, this hypothesis has not been tested for the DLPFC. In fact, increasing the dose of iTBS over the motor cortex can lead to attenuated effects (Gamboa et al., 2010) or even reversal of after-effects (Gamboa et al., 2011). Although it is unclear if these findings can be directly translated to other cortical regions such as the DLPFC, it suggests that further research is needed to define optimal stimulation parameters, specifically pulse dose (Chung et al., 2016, 2015a; Gamboa et al., 2010).

In non-motor areas, excitability changes, such as those induced by iTBS can be assessed through the combined use of transcranial magnetic stimulation (TMS) and electroencephalography (TMS-EEG) (Ilmoniemi and Kičić, 2010; Massimini et al., 2009). TMS-EEG allows the measure of electrophysiological responses elicited by a TMS pulse, such as the TMS-evoked potential (TEP) (Komssi and Kähkönen, 2006) and oscillatory activity called TMS-related oscillations (Pellicciari et al., 2017; Thut et al., 2011). In addition, frequently used paired-pulse TMS measures of cortical inhibition, such as short intra-cortical inhibition (SICI) and long-term intracortical inhibition (LICI), can be assessed over the DLPFC, allowing the measure of iTBS effects on cortical inhibition (Tremblay et al., 2019).

A handful of previous studies have combined prefrontal iTBS with TMS-EEG (Chung et al., 2018a,b, 2019, 2017). Chung and collaborators showed that iTBS induces a modulation of TEP amplitudes (i.e. increased N100 and P200 amplitudes) and of TMS-related cortical oscillations (i.e. theta band ERSP for single-pulse and LICI) in the DLPFC of healthy individuals (Chung et al., 2017). In follow-up studies, iTBS frequency (Chung et al., 2019), intensity (Chung et al., 2018b) and number of stimulation blocks (Chung et al., 2018a) were assessed with TMS-EEG. However, no study has reported the impact of different doses of a single session of iTBS applied to the DLPFC.

This study aims to determine the dose-response of iTBS on left DLPFC cortical activity in healthy volunteers and guide parameter selection for future clinical studies. More specifically, the objective is to compare the effects of three doses frequently employed in clinical trials (600, 1200 and 1800 pulses) on TEP and TMS-related brain oscillations, using single-pulse TMS. Since previous studies have shown that iTBS can modulate intracortical inhibition in the motor cortex (see Chung et al., 2016 for review), prefrontal

LICI and SICI were also measured to further assess the effect of iTBS on GABAergic inhibition. Based on previous studies, it is hypothesized that iTBS will increase cortical activity, reflected by the increased amplitude of TEP components P200 (Chung et al., 2018a, 2017) and N100 (Chung et al., 2018a,b, 2017). It is also hypothesized that iTBS will increase the power of theta band ERSPs following single-pulse and LICI (Chung et al., 2017). Finally, based on motor cortex data (Gamboa et al., 2010), it is hypothesized that 600 pulses may be more effective in modifying cortical activation measures than 1200 and 1800 pulses.

# 2. Materials and methods

#### 2.1. Participants

A total of 14 right-handed healthy volunteers participated in the study (7 females, cohort average: 25.7 ± 5.3 years old). To determine sample size, power analyses were computed using G\*Power Version 3.1.9.4 based on the effect size of previous iTBS/ TMS-EEG studies employing standard iTBS dose over the DLPFC ( $\alpha = 0.05$ ,  $\beta = 0.80$ , f2 = 0.20) (Chung et al., 2018a, 2017).

Inclusion criteria were (a) being a healthy man or woman and (b) aged 18 to 40. Exclusion criteria were (a) lifetime history of psychiatric or neurologic disorder, (b) substance or alcohol abuse/dependence in the past 6 months, (c) pregnancy and/or lactation, (d) presence of a specific contraindication for rTMS, such as history of epileptic seizures or psychotropic medication (Rossi et al., 2009) or (e) hearing loss. All participants provided written informed consent. The study was approved by the Douglas Research Office Research Ethics Board and carried out in accordance with The Code of Ethics of the World Medical Association.

#### 2.2. Procedure

In this crossover randomized study design, each participant underwent 3 different doses of iTBS (600, 1200, 1800 pulses) during 3 different sessions. As a standard practice in the field to avoid carry-over effects (e.g. Chung et al., 2018a, 2017), sessions were separated by at least 7 days (Fig. 1). The session order was randomized and counterbalanced across participants. TMS-EEG measures corresponded to EEG recordings during (a) single-pulse TMS (b) SICI and (c) LICI.

#### 2.3. TMS

Monophasic TMS pulses were delivered using a 70 mm figureof-eight coil and a Deymed DuoMag system (Rogue Resolutions, UK). This system was used for threshold determination at the motor cortex and TMS-EEG measurements over the DLPFC. During stimulation, the coil was held tangentially to the scalp with the handle pointing away from the midline at 45° (Chung et al., 2017; Thomson et al., 2013).

To obtain motor thresholds, two self-adhesive electrodes were positioned on the right first-dorsal interosseous muscle (FDI) and a ground electrode was positioned over the wrist. Electromyography (EMG) signal was recorded using the Brainsight EMG Pod system (Rogue Research Inc., Montreal). A Brainsight Stereotactic Neuronavigation System (Rogue Research Inc., Montreal), based on an average brain model of the Montreal Neurological Institute (MNI), was used for consistent coil positioning. The optimal motor hotspot was defined as the coil position from which TMS produced maximal MEP amplitude. The active and resting motor thresholds (AMT and RMT respectively) were determined for each participant. The AMT was defined as the minimum intensity used to elicit a MEP of at least 200  $\mu$ V in 5 out of 10 trials, while the target muscle



**Fig. 1.** Experimental design and timeline. Each of the 3 sessions included the same phases: (1) a neuronavigation and EEG setup phase, (2) a TMS-EEG pre -TBS phase, (3) an iTBS phase, and (4) a TMS-EEG post-iTBS phase. The TMS-EEG phases included 3 blocks of measurements (80 pulses per block): Single-pulse, SICI and LICI. The order of these measurements was randomized and counterbalanced across participants but kept constant for the 3 sessions for each participant. In the iTBS phase, participants received either 600, 1200 and 1800 pulses of iTBS on three separate visits. The first visit included an additional phase to complete the consent from and to determine stimulation thresholds in order to identify the intensities of stimulation for TMS-EEG and iTBS, which were kept constant for the three visits. Of note, TMS-EEG recordings were conducted immediately after iTBS, thus the study duration slightly differed among the three conditions (600 pulses = 3 min, 900 pulses = 6 min, 1800 pulses = 9 min). EEG = electroencephalography; iTBS = intermittent theta burst stimulation; LICI = long-interval intracortical inhibition; SICI = short-interval intracortical inhibition; TMS = transcranial magnetic stimulation.

was contracted at 10% of the maximal contraction measured with EMG. Visual feedback of EMG activity was provided to participants to ensure consistent muscle contraction. The RMT was defined as the minimum intensity used to elicit a MEP of at least 50  $\mu$ V in 5 out of 10 trials, while the target muscle was at rest. Finally, the intensity was increased until an average 1 mV peak-to-peak amplitude was obtained over 10 trials. To shorten experimental sessions and given that previous studies have shown that motor thresholds display low levels of intra-individual variation across sessions (Ter Braack et al., 2019; Matamala et al., 2018), individual thresholds were determined at session 1 and were kept constant over the three sessions.

Using neuronavigation, the left DLPFC was defined by the MNI coordinates -45, 45, 35, corresponding to the area between BA9 and BA46 (Fitzgerald et al., 2009). Single-pulse TMS was delivered using the intensity that elicited MEPs of 1 mV amplitude (MEP<sub>1mV</sub>) (Noda et al., 2017a; Rogasch et al., 2015). For SICI, a conditioning stimulus (CS) at 80% of the RMT was paired with a test stimulus (TS) of MEP<sub>1mV</sub>, at an inter-stimulus interval (ISI) of 2 ms (Noda et al., 2017a). For LICI, both the CS and TS were applied at a MEP<sub>1mV</sub> intensity, using an ISI of 100 ms (Rogasch et al., 2015). For all experimental sessions, 80 pulses were applied to the left DLPFC at a varying interval ranging from 4–7 s for each of the three neurophysiological measures (i.e. Single-pulse, SICI and LICI). As the paired-pulse TMS device was briefly unavailable during part of data acquisition, SICI and LICI was only conducted in 11 participants.

iTBS was applied to the left DLPFC using a Magstim Super Rapid2 biphasic system with a 70 mm AirFilm cooled-coil (Magstim Company Ltd., U.K.). Since AMT values obtained with both TMS systems were shown to be equivalent in an initial piloting of the study, the AMT values obtained with the DuoMag system were used for iTBS to reduce the duration of the experiment. Fifty Hz triplet bursts were delivered at 5 Hz for 2 s with 10 s interval (Huang et al., 2005). iTBS was applied at an intensity of 80% of AMT, according to the iTBS standard protocol described by Huang and al. (2005), and since results from Chung et al. (2018b) showed that an intensity corresponding to 80% of AMT (i.e. 75% of RMT) is associated with the largest potentiation of cortical activity in the DLPFC. Such intensity also corresponds to initial clinical iTBS studies (Chistyakov et al., 2010; Li et al., 2014). iTBS was applied for a total of 190 s (dose 1, 600 pulses), 380 s (dose 2, 1200 pulses) or 570 s (dose 3, 1800 pulses).

# 2.4. EEG recordings and data preprocessing

EEG signals were recorded with a 64-passive-channel TMScompatible EEG cap (Easycap, BrainVision, Gmb) and a TMScompatible amplifier (BrainAmp DC, BrainVision, Gmb) using an acquisition rate of 5,000 Hz. Electrode impedance was kept below  $5k\Omega$ . Electrodes were referenced online to CPz and grounded to the nasion electrode. EEG wires were arranged in order to minimize artefacts, as recommended by Sekiguchi et al. (2011) and 10–20 measurements were conducted at the beginning of each experimental sessions to ensure consistent EEG cap positioning at key electrode sites (e.g. Cz and F5). To minimize auditory and somatosensory potentials, a white noise was delivered through earphones during EEG recordings, which included specific time-varying frequencies of the TMS click (Massimini et al., 2005), and a thin foam layer was placed under the coil in order to minimize the amount of coil vibration conducted to the skin and therefore, its potential impact on the TEPs (ter Braack et al., 2015).

TMS-EEG data preprocessing was performed using customized scripts in MATLAB (R2019a, The Mathworks, USA), the open source toolbox EEGLAB (Delorme and Makeig, 2004) and Fieldtrip (Oostenveld et al., 2011). TMS-EEG preprocessing included epoching, baseline correction and two rounds of independent component analysis (ICA) applied using the EEGLAB runica algorithm. Specifically, data were epoched around the TMS pulse (-2,000 to 2,000 ms) and baseline corrected (baseline range of -500 to -5ms for single-pulse, -500 to -7 for SICI, and -500 to -105 for LICI). Data from -2 to 15 ms were removed and interpolated. After an automatic rejection of channels near mastoids (i.e.TP9 and TP10), noisy channels were removed via an automated script (i.e. using pop\_rejchan function of the EEGLAB toolbox with an absolute threshold of  $2,5\sigma$  for channels non-ROI channels; and  $3,5\sigma$ for ROI channels). Then, noisy epochs were removed (i.e. using pop\_autorej function of the EEGLAB toolbox). Visual inspection of channels and epochs was also performed after the automated procedure. An average of 7 ± 5 channels were excluded for the singlepulse protocol, 5 ± 5 channels for the SICI protocol and 3 ± 2 channels for the LICI protocol (averages include both mastoid channels that were not gelled). An average of 6.82 (±5.04) epochs were excluded for the single-pulse protocol, 6.85 (±4.31) for the SICI protocol and 5.34 (±4.89) for the LICI protocol. The first ICA round was used to remove TMS-locked artefacts (EMG due to head muscle activation and residual voltage decay) whereas the second ICA was used to remove other artifacts such as eye movements, eye blinks, continuous muscle activation, and residual TMS-locked artefacts (Rogasch and Fitzgerald, 2013; Rogasch et al., 2014). In the first ICA, an average of  $2 \pm 1$  components were removed for the single-pulse protocol,  $2 \pm 1$  for the SICI protocol and  $2 \pm 2$  for the LICI protocol. In the second round of ICA, an average of  $5 \pm 2$ components were removed for the single-pulse protocol,  $4 \pm 2$ for the SICI protocol and 4 ± 3 for the LICI protocol. After removing the TMS high amplitude artifact in the first round of ICA, 1-58 Hz bandpass and 58-62 Hz notch filters were applied (2nd order, zero-phase butterworth filter). Removed channels were interpolated by spherical spline, and data were re-referenced to the average of all scalp electrodes. Finally, a second baseline correction was

applied on epochs (baseline range of -500 to -5 ms for single-pulse, -500 to -7 for SICI, and -500 to -105 for LICI).

#### 2.5. TEP

TEP amplitudes were compared pre- and post-iTBS within the standard peak latency windows as follows: P30 (20–35 ms), N45 (40–50 ms), P60 (55–65 ms), N100 (85–125 ms) and P200 (170–220 ms). These time windows were defined based on the grand average waveform obtained from all doses, as well as on previous literature (Tremblay et al., 2019). All statistical analyses were conducted on a region of interest (ROI) including 5 electrodes surrounding the stimulation target (AF3, F1, F3, FC1, FC3). F5 and FC5, which were situated beneath the coil, were noisy and therefore excluded from the ROI analysis.

For paired-pulse TEPs, the statistical analyses were conducted on the same ROI and within the same standard peak latency windows. To study the effect of paired-pulse on TEPs, the single-pulse was compared with the paired-corrected test pulse (i.e. the second pulse in the paired-pulse condition). This method was chosen in order to directly compare our results with the ones from Chung and collaborators (2017). Firstly, a paired-corrected signal was obtained by time aligning the single-pulse to the conditioning pulse of the paired-pulse (i.e. the first pulse in the paired-pulse condition) and then subtracting the aligned single-pulse from the paired-pulse signal (Rogasch et al., 2015). Secondly, the pairedpulse ratio was calculated for each peak and obtained by subtracting the paired-corrected pulse signal from the single-pulse signal normalized to the TEP overall amplitude (between 20–300 ms), using the following formula (Rogasch et al., 2015).

$$LICI \text{ or } SICI_{peak} = \frac{Singlepulse_{peak} - Paired \ pulse_{peak}}{Singlepulse_{min} - Singlepulse_{max}} x100$$

For each peak of interest, Singlepulse<sub>peak</sub> corresponds to the average single-pulse amplitude within its specific time window. Pairedpulse<sub>peak</sub> corresponds to the average paired-pulse amplitude within its specific time window. Singlepulse<sub>min</sub> corresponds to the minimal value of the signal obtained from 20 to 300 ms. Singlepulse<sub>max</sub> corresponds to the maximal value of the signal obtained from 20 to 300 ms.

#### 2.6. Event related spectral perturbation (ERSP)

Analyses of TMS-related oscillations were conducted on the same ROI. The standard frequency bands were investigated: theta (4–7 Hz), alpha (8–12 Hz), beta (13–29 Hz) and gamma (30–45 Hz), using the following time windows: theta (20–250 ms), alpha (20–150 ms), beta (20–150 ms) and gamma (20–100 ms). These time windows were defined based on previous studies employing similar wider time windows for slower oscillations and narrower time windows for faster oscillations (theta: ranging from 25–50 to 200–250 ms; gamma: ranging from 25–50 to 100–125 ms; beta/alpha: ranging from 25–50 to 200 ms; Chung et al., 2017; Hill et al., 2017; Rogasch et al., 2015) and on the time-frequency representation of the ROI, averaged across conditions and participants (see Section 3.2.1 for Figure 7).

The event related spectral perturbation (ERSP) was obtained by decomposing the TEP signal into a time-frequency domain by using the EEGLAB implementation of Morlet wavelet function (starting at 2 cycles for 3 Hz and linearly increasing cycle number at steps of 0.2 cycle per frequency – ending at 50 Hz) for each trial and electrode of interest. The signal was then averaged over trials. Finally, the power matrix was normalized to baseline (-1000 to -4ms) by dividing the post TMS power by the average power across trials at

each frequency bin. This specific baseline window was chosen to highlight early changes following the TMS pulse.

For paired-pulse TMS, data obtained from the single test pulse were time-aligned and subtracted from the paired-pulse signal to obtain the paired-corrected time-frequency matrix. For each frequency band, the LICI (or SICI) ratio was computed as the difference between the single-pulse data and the paired-corrected data averaged on their time and frequency band windows, and normalized to the mean power across all frequencies, using the following formula (Rogasch et al., 2015):

LICI or 
$$SICI_{freq} = \frac{(Singlepulse_{freq} - Paired \ pulse_{freq})}{Singlepulse_{all}} x100$$

For each peak of interest, Single<sub>freq</sub> corresponds to the average single-pulse oscillations within its specific frequency band and time window. Paired<sub>freq</sub> corresponds to the average paired-pulse oscillations within its specific frequency band and time window. Single<sub>all</sub> corresponds to the average oscillations across all frequencies within the specific time window of each peak.

# 2.7. Statistics

All statistical analyses were performed using the open-source R software Version 3.6.1 (R core Team, Vienna, Austria) and the R Studio package lme4 (Bates et al., 2015).

For single-pulse data, a linear mixed model (LMM) was conducted for each TEP peak of interest (P30, N45, P60, N100 and P200) with dose (600, 1200, 1800 pulses) and time-point (prepost) as within-subject factors. For ERSPs, LMMs were conducted for each frequency band of interest (theta, alpha, beta, gamma) with dose (600, 1200, 1800 pulses) and time-point (pre-post) as within-subject factors.

For paired-pulse data, to first determine the impact of pairedpulse TMS on cortical activations, a series of paired t-tests with Bonferroni correction was performed to compare single-pulse and paired-corrected amplitudes, for each TEP component of interest and frequency band of interest. LMMs were then performed on the paired-pulse ratios, with dose (600, 1200, 1800 pulses) and time-point (pre-post), as within subject factors, for both TEPs and ERSPs.

In order to reduce the number of factors, TEP amplitudes and power of ERSP were also converted into ratios ((post-pre)/pre) and repeated measures ANOVAs were computed with dose (600, 1200, 1800 pulses) as within-subject factors for single- and paired-pulse TEP peaks of interest and ERSPs.

For all LMM, significance was set as  $\alpha = 0.05$  and Tukey's posthoc tests were conducted to explore significant interactions or main effects.

### 3. Results

For single-pulse, SICI and LICI, means and standard deviations from the three iTBS conditions pre/post-iTBS are presented in Supplementary Material (Table S1 and S2). Detailed results for the non-significant interactions between dose and time-point are available in Supplementary Material (Table S3 and S4). Results from repeated measure ANOVAs computed on pre-post ratios are presented in Supplementary Material (Table S5 and S6). Paired ttests were also computed on the grand-average single-pulse TEP amplitude and baseline amplitude, as well as the grand-average single-pulse ERSPs and baseline spectral power to assess the quality of the signal (see Supplementary Table S7 and S8).

#### 3.1. TEPS

#### 3.1.1. Single- pulse

A one-way repeated measures ANOVA with *condition* as factor revealed no significant difference in baseline values for any of the EEG components: P30: F(2,26) = 1.51, p = 0.24,  $\eta 2 = 0.104$ ; N45: F(2,26) = 0.428, p = 0.656,  $\eta 2 = 0.03$ ; P60: F(2,26) = 0.107, p = 0.899,  $\eta 2 = 0.008$ ; N100: F(2,26) = 1.82, p = 0.182,  $\eta 2 = 0.123$ ; P200: F(2,26) = 0.624, p = 0.544,  $\eta 2 = 0.046$ .

Besides, no significant interaction between dose and time-point was found for all components (all p > 0.05). An averaged waveform of all three conditions is shown in Fig. 2A. The averaged single-pulse TEP waveforms for each condition are shown in Supplementary Figure S1, signal-to-noise ratio of early components (20–100 ms) is shown in Supplementary Figure S2 and single-subject TEP waveforms and topographies for each condition are shown in Supplementary Figure S3-S6. A main effect of time-point was found for components P30 ( $F_{1,65} = 10.85$ , p. = 0.002, d = 0.608), N45 ( $F_{1,65} = 8.90$ , p = 0.004, d = 0.526), P60 ( $F_{1,65} = 9.37$ , p = 0.003, d = 0.485), and P200 ( $F_{1,65} = 11.46$ , p = 0.001, d = 0.541) (Fig. 3). All positive components showed a reduction of their amplitudes post-iTBS, whereas the N45 amplitude was increased (Fig. 3).

A main effect of dose was found for the N100 component ( $F_{2,65} = 6.20$ , p = 0.003), reflecting a significant difference between the overall N100 amplitudes (averaged pre-post) for 600 versus 1200 pulses (t(65) = -2.50, p = 0.040, d = -0.33), and 600 versus 1800 pulses (t(65) = -3.40, p < 0.0001, d = -0.07).

# 3.1.2. SICI

At baseline, SICI suppressed the amplitude of P30 (t(32) = 2.79, p = 0.009, d = 0.486), P60 (t(32) = 3.85, p < 0.001, d = 0.671) and P200 (t(32) = 7.21, p < 0.0001, d = 1.255) (Supplementary Fig-

ure S7). For SICI ratios, no significant interaction between dose and time-point was found for all components of interest (all p > 0.05). A main effect of time-point was obtained for P30 ( $F_{1,50} = 9.31$ , p = 0.004, d = 0.711), N45 ( $t_{1,50} = 6.68$ , p = 0.013, d = -0.462) and P200 ( $F_{1,50} = 9.45$ , p = 0.003, d = 0.534). Specifically, iTBS decreased the ratio of P30 and P200, and increased the N45 ratio (Figs. 4 and 5).

A main effect of dose was found for the N100 ( $F_{2,50} = 4.18$ , p = 0.021) and P200 ( $F_{2,50} = 3.39$ , p = 0.041) components. For both components, a significant difference was found in the overall N100 amplitude (average of pre and post) between the 600 and the 1800 doses (N100: t(50) = 2.85, p = 0.017, d = 0.53; P200:  $F_{2,50} = 3.39$ , p = 0.041, d = -0.60).

#### 3.1.3. LICI

At baseline, LICI suppressed the amplitude of P60 (t(32) = 3.59, p = 0.001, d = 0.625) and P200 (t(32) = 7.25, p < 0.0001, d = 1.262) (Supplementary Figure S7). A statistical trend was obtained for the N100, showing a near-significant suppression of its amplitude (t(32) = -2.7, p = 0.011, d = -0.472). Results showed no interaction between dose and time-point (all p > 0.05). Consistent with SICI data, a main effect of time-point was found for the P30 (F<sub>1.50</sub> = 7.66, p = 0.008, d = 0.593) and P200 (F<sub>1.50</sub> = 8.02, p = 0.007, d = 0.463) components, whereby a decrease of the LICI ratio was observed (Figs. 4 and 6).

A main effect of dose was found for the N100 and P200 components (N100:  $F_{2,50} = 9.49$ , p < 0.001; P200:  $F_{2,50} = 3.27$ , p = 0.046). For the N100, Tukey's post-hoc tests showed a significant difference in the overall N100 amplitude (average of pre and post) between the 1800 and 600 doses (t(50) = 4.220, p < 0.0001, d = 0.89), and the 1800 and 1200 doses (t(50) = 3.060, p = 0.010, d = 0.70). For P200, Tukey's Posthoc tests showed a near-significant difference between 600 and 1800 pulses (t(50) = -2,4)



**Fig. 2.** Averaged single-pulse TEP waveform from the three iTBS doses and obtained from the ROI (AF3, F1, F3, FC1, F3). (A) The top panel displays the grand average waveform pre iTBS (continuous line) and post iTBS (dotted line). Shaded area around the curves correspond to the standard error of the mean. Grey shaded areas correspond to the time window of each peak of interest. The missing waveform from 0 to 15 ms corresponds to the data that was removed and interpolated after the TMS pulse. Significant modulations of TEP amplitude post iTBS are obtained for components P30, N45, P60 and P200. (B) The bottom panel shows topographical plots of voltage scalp distribution, for each time window of interest. P30-N45-P60 components activity is localised in the left prefrontal region, while N100 and P200 shows fronto-central activity. \*\* p < 0.001; iTBS = intermittent theta burst stimulation; ROI = region of interest; TEP = transcranial magnetic stimulation evoked potential.



**Fig. 3.** Single-pulse TEPs amplitudes pre- and post-iTBS. Data were obtained from the ROI (AF3, F1, F3, FC1, F3) for each peaks of interest (A) P30, (B) N45, (C) P60, (D) N100 and (E) P200 and among 3 doses (600, 1200 and 1800 pulses). iTBS reduced the amplitude of the P30, P60, P200 components and increased the amplitude of the N45 component. Error bars correspond to the standard error of the mean. \*\* p < 0.001 iTBS = intermittent theta burst stimulation; ROI = region of interest; TEP = transcranial magnetic stimulation evoked potential.



**Fig. 4.** Single-pulse and Paired-pulse TEPs waveform from the three iTBS conditions. (A) The left panel shows SICI data. (B) The right panel shows LICI data. Data were obtained from the ROI (AF3, F1, F3, FC1, F3). The red waveform corresponds to single-pulse data, while the blue one corresponds to corrected paired-pulse data. The continuous line shows the averaged waveform pre-iTBS and the dotted one shows it post-iTBS. The grey shaded areas correspond to the time windows for each peak of interest. At baseline (see bottom of figure), paired-pulse TMS induced a significant suppression of TEP amplitudes for components P60 and P200 (SICI and LICI), and P30 (SICI). Significant modulations of SICI ratios post-iTBS are for obtained for components P30, N45, and P200. Significant modulations of LICI ratios post-iTBS are for obtained for components P30 and P200. Results of paired t-tests: \* p < 0.05 \*\* p < 0.001, \*\*\*\*p < 0.001, # main effect of time-point for linear mixed model p < 0.05, ## main effect of time-point for linear mixed model p < 0.01; iTBS = intermittent theta burst stimulation; LICI = long-interval intracortical inhibition; TEP = transcranial magnetic stimulation evoked potential.

19, p = 0.050, d = -0.59) for the overall P200 amplitude (average of pre and post) (Fig. 6D and Fig. 6E).

# 3.2. ERSP

# 3.2.1. Single-pulse

Consistent with TEP results, no significant interaction between dose and time-point was found for all frequency bands of interest (all p > 0.05). The average ERSP of all three conditions is presented

in Fig. 7. A main effect of time-point was found for the theta band ( $F_{1,65} = 9.91$ , p = 0.002, d = 0.562), whereby the power of the ERSP was reduced post-iTBS (Fig. 8).

A main effect of dose was found for the beta band ( $F_{2,65} = 5.34$ , p = 0.008) and Tukey's post-hoc tests shows a significant difference in the overall ERSP power (averaged pre-post) between the 1200 and 600 doses (t(65) = 2.71, p = 0.023, d = 0.46), and the 1200 and 1800 doses (t(65) = 2.93, p = 0.013, d = 0.50) (Fig. 8C).



**Fig. 5.** SICI TEPs ratios pre and post-iTBS. Data were obtained from the ROI (AF3, F1, F3, FC1, F3) for each peaks of interest (A) P30, (B) N45, (C) P60, (D) N100 and (E) P200 and among 3 doses (600, 1200 and 1800 pulses). Significant effects of time-point are found for P30, N45 and P200 components, \* p < 0.05, \*\* p < 0.01; iTBS = intermittent theta burst stimulation; ROI = region of interest; SICI = short-interval intracortical inhibition; TEP = transcranial magnetic stimulation evoked potential.



**Fig. 6.** LICI TEPs ratios pre and post-iTBS. Data were obtained from the ROI (AF3, F1, F3, FC1, F3) for each peaks of interest (A) P30, (B) N45, (C) P60, (D) N100 and (E) P200 and for 3 doses (600, 1200 and 1800 pulses). Significant effects of time-point are found for P30 and P200 component. \*\* p < 0.01; iTBS = intermittent theta burst stimulation; LICI = long-interval intracortical inhibition; ROI = region of interest; TEP = transcranial magnetic stimulation evoked potential.

# 3.2.2. SICI

At baseline, SICI showed a significant suppression of the power of paired-corrected ERSP in all frequency bands (all p < 0.0001, Supplementary Figure S8). The linear mixed model revealed no significant interaction between dose and time-point and no main effect of time-point for ERSP ratios of all frequency bands (all p > 0.05; Supplementary Figure S9). The average paired-corrected ESRP of all three doses is shown on Fig. 9A.







**Fig. 8.** Single-pulse ERSP amplitudes pre- and post-iTBS. Data were obtained from the ROI (AF3, F1, F3, FC1, F3) for each peaks of interest (A) theta, (B) alpha, (C) beta and (D) gamma and among 3 conditions (600, 1200 and 1800 pulses). A significant effect of time-point is found for the theta band. \*\* p < 0.01; ERSP = event-related spectral perturbation; iTBS = intermittent theta burst stimulation; ROI = region of interest.

3.2.3. LICI

At baseline, a suppression of the power of the paired-corrected ERSP in all frequency bands was found (all p < 0.0001, Supplementary Figure S8). No significant interaction between dose and timepoint was found (all p > 0.05). A main effect of time-point was found for the theta band ( $F_{1,50} = 5.57$ , p = 0.022, d = 0.451), suggesting a reduction of the LICI-related inhibition (Supplementary Figure S10). No main effect of time-point was obtained for the other frequency bands. The average paired-corrected ERSP of the three doses is shown on Fig. 9B.

For the alpha band a main effect of dose was found ( $F_{2,50} = 3.41$ , p = 0.041) and Tukey's post-hoc tests showed a trend for a difference in the overall ERSP ratio for the alpha band (average pre

and post) between the 1200 and 1800 doses (t(50) = -2.33, p = 0.061, d = -0.60).

# 4. Discussion

In recent studies, the standard dose of iTBS has been progressively increased. However, the effects of these alternative protocols on DLPFC activity have never been investigated. This study aimed to systematically compare the effect of the standard iTBS dose (600 pulses) on prefrontal activity in neurotypical participants, with two alternative dosing protocols (1200, 1800 pulses). iTBS was associated with significant changes in DLPFC activity, but these did not differ between doses. This finding is contrary to the



**Fig. 9.** Averaged paired-corrected ERSP from the three iTBS conditions. (A) The top panel shows SICI and the black lines set at time -2 and 0 represents the TMS pulses. (B) The bottom panel represents LICI and the black vertical lines set at time -100 and 0 represents the TMS pulses. For both panels, pre and post iTBS are presented. Each dotted block corresponds to the frequency bands of interest and their specific time window, either theta, alpha, beta and gamma. At baseline, t-tests revealed significant differences between single-pulse and paired-pulse data for all frequency bands. Linear mixed model showed a main effect of time-point for LICI of theta. \*\*\*\*p < 0.0001, #p < 0.05; ERSP = event-related spectral perturbation; TIBS = intermittent theta burst stimulation; LICI = long-interval intracortical inhibition; SICI = short-interval intracortical inhibition; TMS = transcranial magnetic stimulation.

general assumption that increasing dosage also increases aftereffects and contrary to our hypothesis that, based on motor cortex findings, 600 pulses would be superior than higher doses in modulating cortical excitability. Potential mechanisms underlying this result will be discussed.

In addition, our study showed that, regardless of dose, iTBS resulted in (1) a modulation of the amplitude of the majority of TEP components generally pointing towards a decrease of cortical activity (P30, N45, P60, P200), (2) a reduction of SICI- and LICIinduced inhibition on TEP amplitudes (P30, P200), and (3) a decrease in the power of TMS-induced theta oscillations. These data suggest that doubling or tripling the number of iTBS pulses does not result in stronger local potentiation of brain activity in the DLPFC of neurotypical individuals, as assessed by TEPs and ERSPs. Mechanisms responsible for the lack of dose-response will be first discussed, followed by TEP and ERSP changes in response to iTBS and study limitations. Of note, late TEPs components (i.e. N100 and P200) have been demonstrated to be affected by confounding factors such as auditory and sensory potentials (Conde et al., 2019; Gordon et al., 2018) and thus results related to these components need to be interpreted with caution in the current study.

# 4.1. Effect of iTBS dose

In the present study, increasing iTBS dose was not associated with an increase in cortical activity changes. Contrary to a previous motor cortex study, we did not observe a reversal of the induced effect on cortical activity when the dose was increased from 600 to 1200 pulses (Gamboa et al., 2010). Of note, a recent study partially replicated the results from Gamboa and collaborators (2010) in a larger sample, by showing a suppression of corticospinal activity following 1200 pulses (Mccalley et al., 2021). However, they did not obtain the expected facilitation of motor cortex activity associated with 600 pulses or 1800 pulses. Thus, the lack of dose-response obtained in our study supports the

hypothesis of differential mechanisms underlying iTBS between the motor and prefrontal cortices (Daskalakis et al., 2008; Tremblay et al., 2020). Despite these discrepancies, data obtained from studies that target prefrontal and motor regions point in the same direction: the effects of iTBS dose on cortical activity do not appear to be linear, i.e. not proportional to iTBS dose. Previous studies have hypothesized that homeostatic plasticity processes could underlie this absence of linearity (Gamboa et al., 2011, 2010; Nettekoven et al., 2014). The similar neural effects induced by the three iTBS doses could be related to reaching a plateau in the induction of plasticity-like effects (Gamboa et al., 2011, 2010; Nettekoven et al., 2014).

This non-linearity has been reported for other iTBS parameters. For example, in the motor and prefrontal cortices, when a 600pulse block was compared with two 600-pulse blocks, no difference was observed in the modulation of MEPs (Nettekoven et al., 2014) and TEPs (Chung et al., 2018a). In the motor cortex, two 600-pulse blocks were also shown to decrease SICI amplitude, while no effect was found on SICI after one block (Murakami et al., 2012). However, one motor cortex study found a significant increase in the modulation of MEPs after 3 blocks (i.e. 1800 pulses in total), suggesting that iTBS effects could vary depending on the number of blocks applied in motor areas (Nettekoven et al., 2014). In animal studies, dose-response of multiple blocks of iTBS was previously studied, i.e., one to four blocks of 600 pulses at a 15min interval (Volz et al., 2013). As for human studies, their results indicated the lack of linear accumulative effects on markers of glutamate and GABA activity, as well as some specific reversal of induced effects, supporting the hypothesis of homeostatic plasticity (Volz et al., 2013). In addition to pulse blocks, the effect of stimulation intensity was previously studied in humans. Results suggested that the relationship between iTBS intensity and cortical activity in the DLPFC follows an inverted U-curve, whereby an intensity of 75% RMT (~85% AMT) was associated with maximal cortical activity changes, compared to 50% and 100% RMT (Chung et al., 2018b). Notably, a growing number of clinical studies are

using blocks of 1800 pulses (Cole et al., 2020; Li et al., 2020) and higher intensity of stimulation such as 120% RMT (Bakker et al., 2015; Blumberger et al., 2018; Lisanby et al., 2009). The impact of these high-dose and high-intensity paradigms on cortical activity remains to be investigated.

It is important to note that the results of the present study cannot be directly translated to clinical settings as the modulatory effect of iTBS on brain activity may differ in individuals with MDD. For example, MDD was recently associated to altered cortical activity as assessed with TEPs (Voineskos et al., 2019). Given this hypothesis of different baseline levels of activity between individuals with MDD and neurotypical controls, 600 pulses may be insufficient to reach a plateau in the induction of plasticity-like mechanisms in clinical populations, as hypothesized above. The therapeutic response may also originate from the modulation of remote regions connected to the DLPFC, such as the subgenual anterior cingulate cortex (Hadas et al., 2019).

However, our results have clinical implications as, if replicated in a clinical sample, it could suggest that increasing the duration of daily treatments may not be associated with increased neural changes and in turn, potential clinical benefits. This is particularly important as stimulation parameters are often modified in clinical studies without any systematic comparison of the induced clinical and neural effects. Notably, no clinical study has compared the effect of different durations of iTBS on the therapeutic response in depression. Between-studies comparisons are complex, given their heterogeneity (e.g. sample, parameters, criteria for response/remission). However, thus far, similar response rates have been reported in recent trials applying iTBS with 600 (Blumberger et al., 2018) or 1800 pulses (Li et al., 2020). Intensive protocols consisting of multiple iTBS blocks of up to 18,000 pulses per day show particularly high response rates in small samples (~80-90%) (Cole et al., 2020; Williams et al., 2018), emphasizing the importance of investigating the effect of several blocks of iTBS on prefrontal activity in clinical samples.

# 4.2. iTBS effects on TEPs

#### 4.2.1. Single-pulse

Our result show that regardless of the iTBS dose, a decreased amplitude of early positive evoked responses (i.e. P30, P60) was found, pointing towards a reduction of cortical activity. The decreased P30 amplitude post-iTBS is in line with a recent clinical study that reported a reduction of P30 amplitude following left DLPFC high-frequency rTMS treatment (4-weeks, 10 Hz) in MDD patients, which correlated with the therapeutic response (Eshel et al., 2020). Results from intracranial recordings also point towards a suppression of P30 evoked responses following 10 Hz electrical intracranial stimulation (Keller, 2005). While no prefrontal iTBS studies to date quantified P30 responses, an increase in P60 amplitude was reported in a previous iTBS prefrontal study that employed an individualized frequency of stimulation (Chung et al., 2019). Of note, other previous prefrontal iTBS studies by Chung and collaborators (2018a,b, 2017) did not report any change in P60 amplitude, which authors associated with the lower signalto-noise ratio of this component in their sample (Chung et al., 2018b). However, other excitatory neuromodulation paradigms such as transcranial direct stimulation over the DLPFC (Hill et al., 2018) have been associated with increases in P60 amplitude. Some inconsistency is thus seen in the literature in terms of the effect of excitatory neuromodulation paradigms on P60 amplitude, with three studies showing no change, two studies showing an increase in its amplitude and our results pointing towards a decrease in its amplitude. Future replications of these studies in larger samples will help elucidate this.

Although there is currently no consensus regarding the exact mechanism of action, P30 and P60 deflections may be a measure of local cortical excitability levels (Ferreri et al., 2016; Julkunen et al., 2013; Premoli et al., 2019; Vernet et al., 2013; Voineskos et al., 2019). Notably, both the P30 and P60 deflections have been shown to be robust to auditory and somatosensory artefacts (Biabani et al., 2019; Conde et al., 2019; Freedberg et al., 2019; Rocchi et al., 2021). In addition, the P30 component was also shown to be a potential index of cortical reactivity (Fecchio et al., 2017). Besides, studies have showed an association between P60 and cortical excitability (Noda et al., 2017a) again pointing towards an index of cortical excitability. Altogether, our findings suggest that these early components may be a sensitive measure of the neural effects of prefrontal iTBS.

In addition to these early changes pointing towards a reduction of cortical activity, a reduction of P200 amplitude was also found. This is consistent with previous iTBS studies that have reported modulations of P200 amplitude (Casula et al., 2016; Chung et al., 2018a, 2019, 2017), with discrepancies in the direction of the effect. In the DLPFC, while it was initially shown that P200 amplitude was increased by iTBS (Chung et al., 2018a, 2017), a later study using an individualized frequency of iTBS found a decrease (Chung et al., 2019). These discrepancies may indicate that P200 amplitude is less reliable in measuring changes post-iTBS. Although the P200 component has also been associated to cortical excitability (Julkunen et al., 2013; Premoli et al., 2017), it may be particularly sensitive to stimulus salience and remaining auditory activations despite the use of common methodological methods for artefacts reduction (Conde et al., 2019; Gordon et al., 2018). This is reflected in our dataset by topographical maps showing distribution of the signal around the vertex, suggesting a large contribution of sensory activations similar to sham stimulation. Thus, P200 results should be interpreted with caution in the current study, as we cannot exclude that the obtained effects are due to non-specific effects of iTBS on sensory processing.

With regards to negative deflections, our results showed increased N45 amplitude following all three doses, while the N100 amplitude remained unchanged. Motor cortex studies suggest that the N45 component reflects inhibitory mechanisms (Tremblay et al., 2019) more specifically the activity of GABA-A receptors (Farzan et al., 2016; Premoli et al., 2014b). In prefrontal regions, a clinical study reported that N45 amplitude, found to be abnormally high compared to controls, could predict the depressive state of individuals with MDD (Voineskos et al., 2019). Future clinical studies are necessary to determine whether the modulation of N45 by iTBS, along with P30 and P60, plays a role in the reduction of depressive symptoms following treatment.

N100 has also been identified as a potential index of cortical inhibition (Bonnard et al., 2009; Premoli et al., 2014a; Rogasch et al., 2015; Rogasch and Fitzgerald, 2013), and potentially related to GABA-B receptor activity (Fitzgerald et al., 2009). In the present study, N100 was unchanged by iTBS. Although these results are consistent with a recent study (Chung et al., 2019) they contradict other studies that found significant amplitude changes (Chung et al., 2018a,b, 2017, ). The absence of N100 modulation could be explained by confounding auditory and sensory potentials (Conde et al., 2019; Gordon et al., 2018; Rocchi et al., 2021), despite the use of a white noise and piece of foam under the coil, which are also reflected in the topographical maps showing distribution of the signal at the vertex. The use of ear defenders combined with these measures may help future studies in reducing these potentials (Mancuso et al., 2021; Rocchi et al., 2021). An assessment of the level of sensory perception using a likert scale (e.g., sound, vibration, muscle contraction) could also help quantify the contribution of these factors. Moreover, the addition of a sham TMS-EEG condition, either by using a sham coil (Belardinelli et al., 2019) or by using a combination of auditory input, ear defenders and electrical stimulation of the scalp (Mancuso et al., 2021; Rocchi et al., 2021) would provide additional controls. In addition, intersession variations could underlie this finding, as N100 amplitudes were less consistent than the other components, as highlighted by the main effects of dose in statistical analyses. The lack of significant effect on the N100 component in the current study should therefore be interpreted with caution, since some small effects of iTBS may have been masked by large sensory potentials.

#### 4.2.2. Paired-pulse

For SICI, at baseline our results showed a significant reduction in the amplitude of P30, P60 and P200, compared to single-pulse stimulation. Thus, the results are consistent with previous studies (Cash et al., 2017; Noda et al., 2017a) and the hypothesis that SICI reflects inhibition of cortical activity (Rossini et al., 2015; Ziemann and Siebner, 2015). Following iTBS, the inhibitory effect of SICI on P30 and P200 was reduced, while the inhibitory effect of SICI on N45 was increased. To date, no study has quantified the effect of iTBS on SICI via TMS-EEG, thus it is not possible to compare our findings to previous studies. A pharmacological study carried out in the motor cortex suggested a modulation of SICI of N100 following the administration of benzodiazepines, but no change in P30 and P200 suggesting they may reflect different mechanisms (Premoli et al., 2018).

Pre-iTBS, LICI decreased the amplitude of P60 and P200, compared to single-pulse, as previously reported (Opie et al., 2019, 2017, Premoli et al., 2018, 2014a; Rogasch et al., 2015). However, the suppression of the N100 following LICI was only nearsignificant, which is consistent with previous findings showing a suppression of its amplitude by LICI (Opie et al., 2017; Premoli et al., 2014a; Rogasch et al., 2015, 2013). This may be due to the small sample size for paired-pulse conditions which limited our statistical power. With regards to the effects of iTBS on LICI, our data show a decrease in the ratio of LICI of P30 and P200 following iTBS. To date, only one study has quantified LICI following iTBS on the left DLPFC and has shown no change in the ratios of N45. P60. N100 and P200 (Chung et al., 2017). A motor cortex pharmacological study suggested that LICI of P200 is sensitive to the administration of a GABA agonist, such as Baclofen and Diazepam (Premoli et al., 2014b), suggesting that LICI of P200 may be a potential marker of excitation-inhibition balance. Thus, the decrease of LICI is possibly reflecting a modulation of inhibitory activity in the DLPFC.

#### 4.2.3. Potential mechanism

Although motor cortex iTBS is generally associated with an increase in cortical excitability, the effect of iTBS on DLPFC cortical excitability remains poorly understood. In the present study, single-pulse results point towards a potential reduction of cortical activity following prefrontal iTBS, while paired-pulse data suggest a decrease of cortical inhibition. This is in contrast with motor cortex studies and may indicate differential underlying mechanisms. For instance, although the effects are variable across individuals, there is a general consensus that iTBS increases corticospinal excitability as indexed by an increase of MEP amplitude (Suppa et al., 2016). The effect of motor cortex iTBS on measures of cortical inhibition such as SICI and LICI are not as well understood. While some studies have reported facilitation of SICI after iTBS (e.g., Huang et al., 2005; Murakami et al., 2012), others have reported SICI suppression (e.g. Doeltgen and Ridding, 2011), and a recent meta-analysis showed no significant effect on this GABAergic index (Chung et al., 2016). iTBS-induced effects on LICI have not been as frequently studied, and one study reported no significant effect in the motor cortex (Suppa et al., 2008).

To date, no study directly compared the effects of iTBS on prefrontal and motor regions using TMS-EEG. Only two TMS-EEG studies assessed the effect of iTBS on motor cortex TEPs, and showed increased P30 and N100 amplitudes, indicating increased excitation and inhibition (Gedankien et al., 2017; Harrington and Hammond-Tooke, 2015). TMS-EEG studies comparing the effects of iTBS between both regions will allow a better understanding of shared and differential mechanisms of action. Including measures of GABAergic inhibition would also be of interest to obtain a global picture of shared/distinct mechanisms of action.

Altogether, the current findings indicate that iTBS may decrease DLPFC activity via a modulation of the balance between excitation and inhibition. This is in line with a recent magnetic resonance spectroscopy study showing a local modulation of the ratio of GABA and glutamate levels in the left DLPFC following the application of iTBS in healthy controls (Iwabuchi et al., 2017). Animal studies also support the hypothesis that iTBS induces changes in both GABA and glutamate activity, via the expression of specific proteins such as the VGLUT1 and GAD65 (Trippe et al., 2009; Volz et al., 2013). Future multimodal studies combining TMS-EEG with neuroimaging techniques will help further our understanding of the mechanisms of action of prefrontal iTBS.

#### 4.3. iTBS effects on ERSP

None of the three iTBS conditions was superior in modulating the power of ERSP. However, a decrease of the theta band ERSP following iTBS was found for single-pulse and LICI. The theta band was also previously shown to be sensitive to prefrontal iTBS, as modulations of theta power was shown in two previous studies using single pulse (Chung et al., 2018b, 2017) and LICI (Chung et al., 2017), although an increase rather than a decrease was reported. Modulation of the prefrontal theta band post-iTBS have also been previously found with resting EEG (Woźniak-Kwaś niewska et al., 2014). In addition, a case study on iTBS as a treatment for MDD reported a decrease of theta and alpha power following a 4-week treatment (Pellicciari et al., 2017). These results suggest that the theta band is potentially sensitive to the effects of iTBS at the prefrontal level, although the direction of the effects is variable. A potential mechanism is an entrainment effect of iTBS on prefrontal theta oscillations, related to the blocks of burst pulses applied at a theta frequency of 5 Hz (Albouy et al., 2017; Zmeykina et al., 2020).

The neural mechanisms underlying theta waves have been associated with the interaction between the excitatory activity of pyramidal neurons and GABAergic inhibitory activity (Buzsáki, 2002; Xing et al., 2020). In psychiatric disorders such as MDD and schizophrenia, a reduction in theta oscillations has been associated with impaired cortical inhibition and frontal hypoactivation (Hoy et al., 2021; Olbrich and Arns, 2013; Ren et al., 2020). Resting frontal theta oscillations have also been shown to be a potential marker of response to rTMS treatment of MDD (Arns et al., 2015; Woźniak-Kwaśniewska et al., 2015). Investigation of theta waves with TMS-EEG following treatment of iTBS in individuals suffering from MDD will shed light on their potential implication in the therapeutic response.

# 4.4. Limitations

The current findings should be interpreted in the context of limitations. A sham iTBS condition was not included, since the effectiveness of iTBS has already been shown in comparison with sham (Berlim et al., 2017; Chung et al., 2015b). As previously mentioned, the addition of sham TEPs and ear defenders could also have helped mitigate the effect of sensory potentials on TEPs, and help exclude the contribution of potential non-specific effects such as decreases in arousal and attention. For instance, the topographical plots for N100 and P200 components show distribution around the vertex, which strongly suggest that a large proportion of these potentials are associated to sensory activations, as seen in previous studies with sham stimulation (Conde et al., 2019; Gordon et al., 2018; Rocchi et al., 2021). As previously mentioned, we therefore cannot exclude that our N100/P200 results are due to non-specific effects of iTBS on sensory processing.

Further, non-linearity of the evoked activity could have impacted our paired-pulse analyses. Studies comparing different methods of TMS-EEG processing of paired-pulse data (e.g. linear subtraction of peaks versus local mean field power) would help identify the most reliable method. There are also some disadvantages to the ROI method employed in the current study. While this was chosen to directly compare our findings with previous studies that targeted the left DLPFC with iTBS, some dose-response effects in interconnected brain areas may not have been captured. Including an emotional processing task to future studies could also help translate results to clinical applications (Dumitru et al., 2020). Besides, the small sample size could impact the generalization of our results, highlighting the need to replicate findings in a larger cohort. In addition, calibration of the stimulation intensity to the excitability of M1 without accounting for the scalp to cortex distance could have led to over or under stimulation of DLPFC (Stokes et al., 2005; Trojak et al., 2012). Even if the effects of this method have never been systematically tested on the prefrontal cortex, the absence of linear correction for scalp to cortex distance could impact our results.

Besides, we cannot exclude the possibility that some effects of iTBS dose may not have been effectively captured by TMS-EEG. The use of other measures of cortical activity and plasticity such as DLPFC paired-associative stimulation and neuroimaging techniques such as positron emission tomography and resting state connectivity could help further investigate the effects of iTBS dose. Furthermore, residual TMS-related artifact (i.e., decay artifact) can remain even if two rounds of ICA were applied.

Finally, analysis of individual data show that some participants do not show a clear pattern of TMS-induced responses in DLPFC pre- or post-TBS. This raises the possibility that individuals that show clear area-specific responses to TMS may also show greater TBS-induced modulation. While the present study was not adequately powered to address this issue, further studies may determine whether TMS responsiveness can serve as a predictor of TBI-response, which would be of significant clinical value.

#### 5. Conclusion

The increase in the stimulation dose does not seem to be associated with stronger effects on cortical activity, as measured by TEPs and ERSPs. This non-linearity may potentially be linked to mechanisms of homeostatic plasticity, leading to a plateau in the induction of changes in cortical activity. Thus, our findings suggest a local change in the excitation-inhibition balance as a potential mechanism of action of DLPFC iTBS, characterized by decreased excitation and inhibition. Finally, this study underlines the importance of evaluating the effects of iTBS parameters before conducting clinical trials. To translate these results in clinical practice, future studies are needed to assess the effect of iTBS dose in clinical populations, such as MDD.

# **Declaration of Competing Interest**

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: ML reports salary awards including James McGill Professorship, as well as grants from Otsuka Lundbeck Alliance, diaMentis personal fees from Otsuka Canada, personal fees from Lundbeck Canada, grants and personal fees from Janssen, and personal fees from MedAvante-Prophase, outside the submitted work. The remaining authors declare no potential conflict of interest.

#### Acknowledgements

ST was supported by a postdoctoral fellowship of the Canadian Institutes of Health Research (CIHR #338588). This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The team would like to thank Rogue Research Inc. and Brainbox Ltd. for the loan of a paired-pulse TMS device.

# Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2021.12.018.

#### References

- Albouy P, Weiss A, Baillet S, Zatorre RJ. Selective Entrainment of Theta Oscillations in the Dorsal Stream Causally Enhances Auditory Working Memory Performance. Neuron 2017;94(1):193–206.e5. <u>https://doi.org/10.1016/j.neuron.2017.03.015</u>.
- Arns M, Etkin A, Hegerl U, Williams LM, DeBattista C, Palmer DM, Fitzgerald PB, Harris A, deBeuss R, Gordon E. Frontal and rostral anterior cingulate (rACC) theta EEG in depression: Implications for treatment outcome? Eur Neuropsychopharmacol 2015;25(8):1190–200. <u>https://doi.org/10.1016/i.euroneuro.2015.03.007</u>.
- Baeken C, Duprat R, Wu G-R, De Raedt R, van Heeringen K. Subgenual Anterior Cingulate-Medial Orbitofrontal Functional Connectivity in Medication-Resistant Major Depression: A Neurobiological Marker for Accelerated Intermittent Theta Burst Stimulation Treatment? Biol Psychiatry Cogn Neurosci Neuroimaging 2017;2(7):556–65. <u>https://doi.org/10.1016/j. bpsc.2017.01.001</u>.
- Bakker N, Shahab S, Giacobbe P, Blumberger DM, Daskalakis ZJ, Kennedy SH, et al. RTMS of the dorsomedial prefrontal cortex for major depression: Safety, tolerability, effectiveness, and outcome predictors for 10 Hz versus intermittent theta-burst stimulation. Brain Stimul 2015;8:208–15. <u>https://doi.org/10.1016/j. brs.2014.11.002</u>.
- Bates D, Mächler M, Bolker BM, Walker SC. Fitting linear mixed-effects models using lme4. J Stat Softw 2015;67. <u>https://doi.org/10.18637/jss.v067.i01</u>.
- Belardinelli P, Biabani M, Blumberger DM, Bortoletto M, Casarotto S, David O, Desideri D, Etkin A, Ferrarelli F, Fitzgerald PB, Fornito A, Gordon PC, Gosseries O, Harquel S, Julkunen P, Keller CJ, Kimiskidis VK, Lioumis P, Miniussi C, Rosanova M, Rossi S, Sarasso S, Wu W, Zrenner C, Daskalakis ZJ, Rogasch NC, Massimini M, Ziemann U, Ilmoniemi RJ. Reproducibility in TMS–EEG studies: A call for data sharing, standard procedures and effective experimental control. Brain Stimul 2019;12(3):787–90. https://doi.org/10.1016/j.brs.2019.01.010.
- Berlim MT, McGirr A, Rodriguez dos Santos N, Tremblay S, Martins R. Efficacy of theta burst stimulation (TBS) for major depression: An exploratory metaanalysis of randomized and sham-controlled trials. J Psychiatr Res 2017;90:102–9. <u>https://doi.org/10.1016/i.jpsychires.2017.02.015</u>.
- Biabani M, Fornito A, Mutanen TP, Morrow J, Rogasch NC. Characterizing and minimizing the contribution of sensory inputs to TMS-evoked potentials. Brain Stimul 2019;12(6):1537–52. <u>https://doi.org/10.1016/j.brs.2019.07.009</u>.
- Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, Knyahnytska Y, Kennedy SH, Lam RW, Daskalakis ZJ, Downar J. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet 2018;391(10131):1683–92. <u>https://doi.org/10.1016/S0140-6736(18)</u> 30295-2.
- Bonnard M, Spieser L, Meziane HB, De Graaf JB, Pailhous J. Prior intention can locally tune inhibitory processes in the primary motor cortex: Direct evidence from combined TMS-EEG. Eur J Neurosci 2009;30:913–23. <u>https://doi.org/10.1111/j. i.1460-9568.2009.06864.x.</u>
- ter Braack EM, de Goede AA, van Putten MJAM. Resting Motor Threshold, MEP and TEP Variability During Daytime. Brain Topogr 2019;32(1):17–27. <u>https://doi.org/10.1007/s10548-018-0662-7</u>.
- ter Braack EM, de Vos CC, van Putten MJAM. Masking the Auditory Evoked Potential in TMS-EEG: A Comparison of Various Methods. Brain Topogr 2015;28 (3):520-8. <u>https://doi.org/10.1007/s10548-013-0312-z</u>.
- Buzsáki G. Theta oscillations in the hippocampus. Neuron 2002;33(3):325-40.
- Capocchi G, Zampolini M, Larson J. Theta burst stimulation is optimal for induction of LTP at both apical and basal dendritic synapses on hippocampal CA1 neurons. Brain Res 1992;591(2):332–6. <u>https://doi.org/10.1016/0006-8993(92)91715-0</u>.
- Cash RFH, Noda Y, Zomorrodi R, Radhu N, Farzan F, Rajji TK, Fitzgerald PB, Chen R, Daskalakis ZJ, Blumberger DM. Characterization of Glutamatergic and GABA A-Mediated Neurotransmission in Motor and Dorsolateral Prefrontal Cortex Using

#### M. Desforges, I. Hadas, B. Mihov et al.

Paired-Pulse TMS-EEG. Neuropsychopharmacology 2017;42(2):502–11. https:// doi.org/10.1038/npp.2016.133.

- Casula EP, Pellicciari MC, Ponzo V, Stampanoni Bassi M, Veniero D, Caltagirone C, et al. Cerebellar theta burst stimulation modulates the neural activity of interconnected parietal and motor areas. Sci Rep 2016;6:1–10. <u>https://doi.org/ 10.1038/srep36191</u>.
- Caulfield KA. Is accelerated, high-dose theta burst stimulation a panacea for treatment-resistant depression? J Neurophysiol 2020;123(1):1–3. <u>https://doi. org/10.1152/jn.00537.2019</u>.
- Chistyakov AV, Rubicsek O, Kaplan B, Zaaroor M, Klein E. Safety, tolerability and preliminary evidence for antidepressant efficacy of theta-burst transcranial magnetic stimulation in patients with major depression. Int J Neuropsychopharmacol 2010;13:387–93. <u>https://doi.org/10.1017/ \$1461145710000027</u>.
- Chung SW, Hill AT, Rogasch NC, Hoy KE, Fitzgerald PB. Use of theta-burst stimulation in changing excitability of motor cortex: A systematic review and meta-analysis. Neurosci Biobehav Rev 2016;63:43–64. <u>https://doi.org/10.1016/ i.neubiorev.2016.01.008</u>.
- Chung SW, Hoy KE, Fitzgerald PB. Theta-burst stimulation: A new form of tms treatment for depression? Depress Anxiety 2015a;32(3):182–92. <u>https://doi.org/10.1002/da.22335</u>.
- Chung SW, Lewis BP, Rogasch NC, Saeki T, Thomson RH, Hoy KE, Bailey NW, Fitzgerald PB. Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation: A TMS-EEG study. Clin Neurophysiol 2017;128(7):1117–26. <u>https://doi.org/10.1016/</u> j.clinph.2017.04.005.
- Chung SW, Rogasch NC, Hoy KE, Fitzgerald PB. The effect of single and repeated prefrontal intermittent theta burst stimulation on cortical reactivity and working memory. Brain Stimul 2018a;11(3):566–74. <u>https://doi.org/10.1016/j. brs.2018.01.002</u>.
- Chung SW, Rogasch NC, Hoy KE, Fitzgerald PB. Measuring brain stimulation induced changes in cortical properties using TMS-EEG. Brain Stimul 2015b;8 (6):1010–20. <u>https://doi.org/10.1016/j.brs.2015.07.029</u>.
- Chung SW, Rogasch NC, Hoy KE, Sullivan CM, Cash RFH, Fitzgerald PB. Impact of different intensities of intermittent theta burst stimulation on the cortical properties during TMS-EEG and working memory performance. Hum Brain Mapp 2018b;39(2):783–802. <u>https://doi.org/10.1002/hbm.23882</u>.
- Chung SW, Sullivan CM, Rogasch NC, Hoy KE, Bailey NW, Cash RFH, Fitzgerald PB. The effects of individualised intermittent theta burst stimulation in the prefrontal cortex: A TMS-EEG study. Hum Brain Mapp 2019;40(2):608–27. https://doi.org/10.1002/hbm.24398.
- Cole EJ, Stimpson KH, Bentzley BS, Gulser M, Cherian K, Tischler C, Nejad R, Pankow H, Choi E, Aaron H, Espil FM, Pannu J, Xiao X, Duvio D, Solvason HB, Hawkins J, Guerra A, Jo B, Raj KS, Phillips AL, Barmak F, Bishop JH, Coetzee JP, DeBattista C, Keller J, Schatzberg AF, Sudheimer KD, Williams NR. Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression. Am J Psychiatry 2020;177(8):716–26. <a href="https://doi.org/10.1176/appi.aip.2019.19070720">https://doi.org/10.1176/appi.aip.2019.19070720</a>
- Conde V, Tomasevic L, Akopian I, Stanek K, Saturnino GB, Thielscher A, Bergmann TO, Siebner HR. The non-transcranial TMS-evoked potential is an inherent source of ambiguity in TMS-EEG studies. Neuroimage 2019;185:300–12. https://doi.org/10.1016/i.neuroimage.2018.10.052.
- Cristancho P, Kamel L, Araque M, Berger J, Blumberger DM, Miller JP, Barch DM, Lenze EJ. iTBS to Relieve Depression and Executive Dysfunction in Older Adults: An Open Label Study. Am J Geriatr Psychiatry 2020;28(11):1195–9. <u>https://doi.org/10.1016/j.jagp.2020.03.001</u>.
- Daskalakis ZJ, Farzan F, Barr MS, Maller JJ, Chen R, Fitzgerald PB. Long-interval cortical inhibition from the dorsolateral prefrontal cortex: A TMS-EEG study. Neuropsychopharmacology 2008;33(12):2860–9. <u>https://doi.org/10.1038/ npp.2008.22</u>.
- Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 2004;134:9–21. <u>https://doi.org/10.1016/j.techsoc.2013.07.004</u>.
- Dhami P, Knyahnytska Y, Atluri S, Lee J, Courtney DB, Croarkin PE, Blumberger DM, Daskalakis ZJ, Farzan F. Feasibility and clinical effects of theta burst stimulation in youth with major depressive disorders: An open-label trial. J Affect Disord 2019;258:66–73. <u>https://doi.org/10.1016/j.jad.2019.07.084</u>.
- Doeltgen SH, Ridding MC. Modulation of cortical motor networks following primed theta burst transcranial magnetic stimulation. Exp brain Res Exp 2011;215(3– 4):199–206. <u>https://doi.org/10.1007/s00221-011-2886-6</u>.
- Dumitru A, Rocchi L, Saini F, Rothwell JC, Roiser JP, David AS, Richieri RM, Lewis G, Lewis G. Influence of theta-burst transcranial magnetic stimulation over the dorsolateral prefrontal cortex on emotion processing in healthy volunteers. Cogn Affect Behav Neurosci 2020;20(6):1278–93. <u>https://doi.org/10.3758/ s13415-020-00834-0</u>.
- Duprat R, De Raedt R, Wu GR, Baeken C. Intermittent theta burst stimulation increases reward responsiveness in individuals with higher hedonic capacity. Front Hum Neurosci 2016;10:1–11. <u>https://doi.org/10.3389/</u> fnhum.2016.00294.
- Eshel N, Keller CJ, Wu W, Jiang J, Mills-Finnerty C, Huemer J, Wright R, Fonzo GA, Ichikawa N, Carreon D, Wong M, Yee A, Shpigel E, Guo Yi, McTeague L, Maron-Katz A, Etkin A. Global connectivity and local excitability changes underlie antidepressant effects of repetitive transcranial magnetic stimulation. Neuropsychopharmacology 2020;45(6):1018–25. <u>https://doi.org/10.1038/</u> <u>s41386-020-0633-z</u>.

- Farzan F, Vernet M, Shafi MMD, Rotenberg A, Daskalakis ZJ, Pascual-Leone A. Characterizing and Modulating Brain Circuitry through Transcranial Magnetic Stimulation Combined with Electroencephalography. Front Neural Circuits 2016;10. <u>https://doi.org/10.3389/fncir.2016.00073</u>.
- Fecchio M, Pigorini A, Comanducci A, Sarasso S, Casarotto S, Premoli I, et al. The spectral features of EEG responses to transcranial magnetic stimulation of the primary motor cortex depend on the amplitude of the motor evoked potentials. BioRxiv 2017:1–15. <u>https://doi.org/10.1101/133769</u>.
- Ferreri F, Vecchio F, Vollero L, Guerra A, Petrichella S, Ponzo D, Määtta S, Mervaala E, Könönen M, Ursini F, Pasqualetti P, Iannello G, Rossini PM, Di Lazzaro V. Sensorimotor cortex excitability and connectivity in Alzheimer's disease: A TMS-EEG Co-registration study. Hum Brain Mapp 2016;37(6):2083–96. <u>https:/// doi.org/10.1002/hbm.23158</u>.
- Fitzgerald PB, Maller JJ, Hoy KE, Thomson R, Daskalakis ZJ. Exploring the optimal site for the localization of dorsolateral prefrontal cortex in brain stimulation experiments. Brain Stimul 2009;2(4):234–7. <u>https://doi.org/10.1016/j. brs.2009.03.002</u>.
- Freedberg M, Reeves J, Hussain S, Zaghloul K, Wassermann E. Identifying site- and stimulation-specific TMS-evoked EEG potentials using a quantitative cosine similarity metric. BioRxiv 2019;612499. <u>https://doi.org/10.1101/612499</u>.
- Gamboa OL, Antal A, Laczo B, Moliadze V, Nitsche MA, Paulus W. Impact of repetitive theta burst stimulation on motor cortex excitability. Brain Stimul 2011;4(3):145-51. <u>https://doi.org/10.1016/j.brs.2010.09.008</u>.
- Gamboa OL, Antal A, Moliadze V, Paulus W. Simply longer is not better: Reversal of theta burst after-effect with prolonged stimulation. Exp Brain Res 2010;204 (2):181-7. <u>https://doi.org/10.1007/s00221-010-2293-4</u>.
- Gedankien T, Fried PJ, Pascual-Leone A, Shafi MM. Intermittent theta-burst stimulation induces correlated changes in cortical and corticospinal excitability in healthy older subjects. Clin Neurophysiol 2017;128 (12):2419–27. <u>https://doi.org/10.1016/j.clinph.2017.08.034</u>.
- Gordon PC, Desideri D, Belardinelli P, Zrenner C, Ziemann U. Comparison of cortical EEG responses to realistic sham versus real TMS of human motor cortex. Brain Stimul 2018;11(6):1322–30. <u>https://doi.org/10.1016/j.brs.2018.08.003</u>.
- Hadas I, Sun Y, Lioumis P, Zomorrodi R, Jones B, Voineskos D, Downar J, Fitzgerald PB, Blumberger DM, Daskalakis ZJ. Association of Repetitive Transcranial Magnetic Stimulation Treatment With Subgenual Cingulate Hyperactivity in Patients With Major Depressive Disorder: A Secondary Analysis of a Randomized Clinical Trial. JAMA Netw Open 2019;2(6):e195578. <u>https://doi. org/10.1001/jamanetworkopen.2019.5578</u>.
- Harrington A, Hammond-Tooke GD, Tremblay F. Theta burst stimulation of the cerebellum modifies the TMS-evoked N100 potential, a marker of GABA inhibition. PLoS One 2015;10(11):e0141284. <u>https://doi.org/10.1371/journal.pone.0141284</u>.
- Hill AT, Rogasch NC, Fitzgerald PB, Hoy KE. Effects of prefrontal bipolar and highdefinition transcranial direct current stimulation on cortical reactivity and working memory in healthy adults. NeuroImage 2017;152:142–57. <u>https://doi. org/10.1016/i.neuroimage.2017.03.001</u>.
- Hill AT, Rogasch NC, Fitzgerald PB, Hoy KE. Effects of single versus dual-site High-Definition transcranial direct current stimulation (HD-tDCS) on cortical reactivity and working memory performance in healthy subjects. Brain Stimul 2018;11(5):1033–43. <u>https://doi.org/10.1016/j.brs.2018.06.005</u>.
- Hoy KE, Coyle H, Gainsford K, Hill AT, Bailey NW, Fitzgerald PB. Investigating neurophysiological markers of impaired cognition in schizophrenia.. Schizophr Res 2021;233:34–43. <u>https://doi.org/10.1016/j.schres.2021.06.025</u>.
- Hsu Y-F, Liao K-K, Lee P-L, Tsai Y-A, Yeh C-L, Lai K-L, Huang Y-Z, Lin Y-Y, Lee I-H. Intermittent theta burst stimulation over primary motor cortex enhances movement-related beta synchronisation. Clin Neurophysiol 2011;122 (11):2260-7. https://doi.org/10.1016/j.clinph.2011.03.027.
- Huang Y-Z, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45(2):201–6. <u>https://doi.org/10.1016/j.neuron.2004.12.033</u>.
- Huang YZ, Rothwell JC, Lu CS, Chuang WL, Lin WY, Chen RS. Reversal of plasticitylike effects in the human motor cortex. J Physiol 2010;588:3683–93. <u>https://doi. org/10.1113/jphysiol.2010.191361</u>.
- Ilmoniemi RJ, Kičić D. Methodology for combined TMS and EEG. Brain Topogr 2010;22(4):233–48. <u>https://doi.org/10.1007/s10548-009-0123-4</u>.
  Iwabuchi SJ, Auer DP, Liddle PF, Lankappa ST, Palaniyappan L. Targeted transcranial
- Iwabuchi SJ, Auer DP, Liddle PF, Lankappa ST, Palaniyappan L. Targeted transcranial theta-burst stimulation alters fronto-insular network and prefrontal GABA.. Neuroimage 2017;146:395–403. <u>https://doi.org/10.1016/i.</u> neuroimage.2016.09.043.
- Julkunen P, Säisänen L, Könönen M, Vanninen R, Kälviäinen R, Mervaala E. TMS-EEG reveals impaired intracortical interactions and coherence in Unverricht-Lundborg type progressive myoclonus epilepsy (EPM1). Epilepsy Res 2013;106(1-2):103–12. <u>https://doi.org/10.1016/j.eplepsyres.2013.04.001</u>.
- Keller MB. Issues in Treatment-Resistant Depression. J Clin Psychiatry 2005;66:5– 12.
- Komssi S, Kähkönen S. The novelty value of the combined use of electroencephalography and transcranial magnetic stimulation for neuroscience research. Brain Res Rev 2006;52(1):183–92. <u>https://doi.org/ 10.1016/i.brainresrev.2006.01.008</u>.
- Li C-T, Cheng C-M, Chen M-H, Juan C-H, Tu P-C, Bai Y-M, Jeng J-S, Lin W-C, Tsai S-J, Su T-P. Antidepressant Efficacy of Prolonged Intermittent Theta Burst Stimulation Monotherapy for Recurrent Depression and Comparison of Methods for Coil Positioning: A Randomized, Double-Blind. Sham-Controlled Study. Biol Psychiatry 2020;87(5):443–50. <u>https://doi.org/10.1016/j. biopsych.2019.07.031</u>.

#### M. Desforges, I. Hadas, B. Mihov et al.

- Li CT, Chen MH, Juan CH, Huang HH, Chen LF, Hsieh JC, et al. Efficacy of prefrontal theta-burst stimulation in refractory depression: A randomized sham-controlled study. Brain 2014;137:2088–98. https://doi.org/10.1093/brain/awu109.
- Li CT, Chen MH, Juan CH, Liu RS, Lin WC, Bai YM, et al. Effects of prefrontal thetaburst stimulation on brain function in treatment-resistant depression: A randomized sham-controlled neuroimaging study. Brain Stimul 2018;11:1054–62. https://doi.org/10.1016/j.brs.2018.04.014.
- Lisanby SH, Husain MM, Rosenquist PB, Maixner D, Gutierrez R, Krystal A, Gilmer W, Marangell LB, Aaronson S, Daskalakis ZJ, Canterbury R, Richelson E, Sackeim HA, George MS. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: Clinical predictors of outcome in a multisite, randomized controlled clinical trial. Neuropsychopharmacology 2009;34(2):522–34. https://doi.org/10.1038/npp.2008.118.
- Mancuso M, Sveva V, Cruciani A, Brown K, Ibáñez J, Rawji V, Casula E, Premoli I, D'Ambrosio S, Rothwell J, Rocchi L. Transcranial evoked potentials can be reliably recorded with active electrodes. Brain Sci 2021;11(2):145.
- Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G. Neuroscience: Breakdown of cortical effective connectivity during sleep. Science 2005;309 (5744):2228–32.
- Massimini M, Tononi G, Huber R. Slow waves, synaptic plasticity and information processing: Insights from transcranial magnetic stimulation and high-density EEG experiments. Eur J Neurosci 2009;29:1761–70. <u>https://doi.org/10.1111/ i.1460-9568.2009.06720.x</u>.
- Mastroeni C, Bergmann TO, Rizzo V, Ritter C, Klein C, Pohlmann I, et al. Brain-Derived Neurotrophic Factor - A Major Player in Stimulation-Induced Homeostatic Metaplasticity of Human Motor Cortex? PLoS One 2013;8. https://doi.org/10.1371/journal.pone.0057957.
- Matamala JM, Howells J, Dharmadasa T, Trinh T, Ma Y, Lera L, Vucic S, Burke D, Kiernan MC. Inter-session reliability of short-interval intracortical inhibition measured by threshold tracking TMS. Neurosci Lett 2018;674:18–23. <u>https:// doi.org/10.1016/j.neulet.2018.02.065</u>.
- Mccalley DM, Lench DH, Doolittle JD, Imperatore JP, Hoffman M, Hanlon CA. Determining the optimal pulse number for theta burst induced change in cortical excitability. Sci Rep 2021:1–9. <u>https://doi.org/10.1038/s41598-021-87916-2</u>.
- Murakami T, Müller-Dahlhaus F, Lu M-K, Ziemann U. Homeostatic metaplasticity of corticospinal excitatory and intracortical inhibitory neural circuits in human motor cortex. J Physiol 2012;590:5765–81. <u>https://doi.org/10.1113/</u> iphysiol.2012.238519.
- Nettekoven C, Volz LJ, Kutscha M, Pool E-M, Rehme AK, Eickhoff SB, Fink GR, Grefkes C. Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. J Neurosci 2014;34 (20):6849–59. <u>https://doi.org/10.1523/INEUROSCI.4993-13.2014</u>.
- Noda Y, Zomorrodi R, Cash RFH, Barr MS, Farzan F, Rajji TK, Chen R, Daskalakis ZJ, Blumberger DM. Characterization of the influence of age on GABAA and glutamatergic mediated functions in the dorsolateral prefrontal cortex using paired-pulse TMS-EEG. Aging (Albany NY) 2017a;9(2):556–72.
- Olbrich S, Arns M. EEG biomarkers in major depressive disorder: Discriminative power and prediction of treatment response. Int Rev Psychiatry 2013;25 (5):604–18. <u>https://doi.org/10.3109/09540261.2013.816269</u>.
- Oostenveld R, Fries P, Maris E, Schoffelen J-M. Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011;2011:1–9. <u>https://doi.org/10.1155/2011/156869</u>.
- Opie GM, Foo N, Killington M, Ridding MC, Semmler JG. Transcranial magnetic stimulation-electroencephalography measures of cortical neuroplasticity are altered after mild traumatic brain injury. J Neurotrauma 2019;36(19):2774–84. https://doi.org/10.1089/neu.2018.6353.
- Opie GM, Rogasch NC, Goldsworthy MR, Ridding MC, Semmler JG. Investigating TMS-EEG Indices of Long-Interval Intracortical Inhibition at Different Interstimulus Intervals. Brain Stimul 2017;10(1):65–74. <u>https://doi.org/ 10.1016/i.brs.2016.08.004</u>.
- Pellicciari MC, Ponzo V, Caltagirone C, Koch G. Restored Asymmetry of Prefrontal Cortical Oscillatory Activity after Bilateral Theta Burst Stimulation Treatment in a Patient with Major Depressive Disorder: A TMS-EEG Study. Brain Stimul 2017;10(1):147–9. <u>https://doi.org/10.1016/j.brs.2016.09.006</u>.
- Plewnia C, Pasqualetti P, Große S, Schlipf S, Wasserka B, Zwissler B, Fallgatter A. Treatment of major depression with bilateral theta burst stimulation: A randomized controlled pilot trial. J Affect Disord 2014;156:219–23. <u>https:// doi.org/10.1016/j.jad.2013.12.025</u>.
- Prasser J, Schecklmann M, Poeppl TB, Frank E, Kreuzer PM, Hajak G, Rupprecht R, Landgrebe M, Langguth B. Bilateral prefrontal rTMS and theta burst TMS as an add-on treatment for depression: A randomized placebo controlled trial. World J Biol Psychiatry 2015;16(1):57–65. <u>https://doi.org/10.3109/</u> 15622975.2014.964768.
- Premoli I, Biondi A, Carlesso S, Rivolta D, Richardson MP. Lamotrigine and levetiracetam exert a similar modulation of TMS-evoked EEG potentials. Epilepsia 2017;58(1):42–50. <u>https://doi.org/10.1111/epi.13599</u>.
- Premoli I, Castellanos N, Rivolta D, Belardinelli P, Bajo R, Zipser C, Espenhahn S, Heidegger T, Muller-Dahlhaus F, Ziemann U. TMS-EEG signatures of GABAergic neurotransmission in the human cortex. J Neurosci 2014a;34(16):5603–12. https://doi.org/10.1523/JNEUROSCI.5089-13.2014.
- Premoli I, Király J, Müller-Dahlhaus F, Zipser CM, Rossini P, Zrenner C, Ziemann U, Belardinelli P. Short-interval and long-interval intracortical inhibition of TMSevoked EEG potentials. Brain Stimul 2018;11(4):818–27. <u>https://doi.org/</u> 10.1016/i.brs.2018.03.008.

- Premoli I, Rivolta D, Espenhahn S, Castellanos N, Belardinelli P, Ziemann U, Müller-Dahlhaus F. Characterization of GABAB-receptor mediated neurotransmission in the human cortex by paired-pulse TMS-EEG. Neuroimage 2014b;103:152–62. <u>https://doi.org/10.1016/j.neuroimage.2014.09.028</u>.
- Premoli I, Rossini PG, Goldberg PY, Posadas K, Green L, Yogo N, Pimstone S, Abela E, Beatch GN, Richardson MP. TMS as a pharmacodynamic indicator of cortical activity of a novel anti-epileptic drug, XEN1101. Ann Clin Transl Neurol 2019;6 (11):2164–74. <u>https://doi.org/10.1002/acn3.50896</u>
- Ren Y, Pan L, Du X, Li X, Hou Y, Bao J, Song Y. Theta oscillation and functional connectivity alterations related to executive control in temporal lobe epilepsy with comorbid depression. Clin Neurophysiol 2020;131(7):1599–609. <u>https:// doi.org/10.1016/j.clinph.2020.03.038</u>.
- Rocchi L, Di Santo A, Brown K, Ibáñez J, Casula E, Rawji V, Di Lazzaro V, Koch G, Rothwell J. Disentangling EEG responses to TMS due to cortical and peripheral activations. Brain Stimul 2021;14(1):4–18. <u>https://doi.org/10.1016/j. brs.2020.10.011</u>.
- Rogasch NC, Daskalakis ZJ, Fitzgerald PB. Cortical inhibition of distinct mechanisms in the dorsolateral prefrontal cortex is related to working memory performance: A TMS-EEG study. Cortex 2015;64:68–77. <u>https://doi.org/ 10.1016/j.cortex.2014.10.003</u>.
- Rogasch NC, Daskalakis ZJ, Fitzgerald PB. Mechanisms underlying long-interval cortical inhibition in the human motor cortex: A TMS-EEG study. J Neurophysiol 2013;109(1):89–98. <u>https://doi.org/10.1152/jn.00762.2012</u>.
- Rogasch NC, Fitzgerald PB. Assessing cortical network properties using TMS-EEG. Hum Brain Mapp 2013;34(7):1652–69. <u>https://doi.org/10.1002/hbm.22016</u>.
- Rogasch NC, Thomson RH, Farzan F, Fitzgibbon BM, Bailey NW, Hernandez-Pavon JC, Daskalakis ZJ, Fitzgerald PB. Removing artefacts from TMS-EEG recordings using independent component analysis: Importance for assessing prefrontal and motor cortex network properties. Neuroimage 2014;101:425–39. <u>https://doi. org/10.1016/j.neuroimage.2014.07.037</u>.
- Rossi S, Hallett M, Rossini PM, Pascual-Leone A. The Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120:2008–39. <u>https://doi.org/10.1016/</u> i.clinph.2009.08.016.Rossi.
- Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, Di Lazzaro V, Ferreri F, Fitzgerald PB, George MS, Hallett M, Lefaucheur JP, Langguth B, Matsumoto H, Miniussi C, Nitsche MA, Pascual-Leone A, Paulus W, Rossi S, Rothwell JC, Siebner HR, Ugawa Y, Walsh V, Ziemann U. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application: An updated report from an I.F.C.N. Committee. Clin Neurophysiol 2015;126 (6):1071–107. https://doi.org/10.1016/j.clinph.2015.02.001.
- Sekiguchi H, Takeuchi S, Kadota H, Kohno Y, Nakajima Y. TMS-induced artifacts on EEG can be reduced by rearrangement of the electrode's lead wire before recording. Clin Neurophysiol 2011;122(5):984–90. <u>https://doi.org/10.1016/ i.clinph.2010.09.004</u>.
- Staubli U, Lynch G. Stable hippocampal long-term potentiation elicited by "theta" pattern stimulation. Brain Res 1987;435(1-2):227–34. <u>https://doi.org/10.1016/</u> 0006-8993(87)91605-2.
- Stokes MG, Chambers CD, Gould IC, Henderson TR, Janko NE, Allen NB, Mattingley JB. Simple metric for scaling motor threshold based on scalp-cortex distance: Application to studies using transcranial magnetic stimulation. J Neurophysiol 2005;94(6):4520–7. <u>https://doi.org/10.1152/jn.00067.2005</u>.
- Suppa A, Huang Y-Z, Funke K, Ridding MC, Cheeran B, Di Lazzaro V, Ziemann U, Rothwell JC. Ten Years of Theta Burst Stimulation in Humans: Established Knowledge. Unknowns and Prospects. Brain Stimul 2016;9(3):323–35. <u>https:// doi.org/10.1016/j.brs.2016.01.006</u>.
- Suppa A, Ortu E, Zafar N, Deriu F, Paulus W, Berardelli A, Rothwell JC. Theta burst stimulation induces after-effects on contralateral primary motor cortex excitability in humans. J Physiol 2008;586(18):4489–500. <u>https://doi.org/ 10.1113/iphysiol.2008.156596</u>.
- Thomson RH, Cleve TJ, Bailey NW, Rogasch NC, Maller JJ, Daskalakis ZJ, Fitzgerald PB. Blood oxygenation changes modulated by coil orientation during prefrontal transcranial magnetic stimulation. Brain Stimul 2013;6(4):576–81. <u>https://doi.org/10.1016/i.brs.2012.12.001</u>.
- Thut G, Veniero D, Romei V, Miniussi C, Schyns P, Gross J. Rhythmic TMS causes local entrainment of natural oscillatory signatures. Curr Biol 2011;21 (14):1176–85. <u>https://doi.org/10.1016/j.cub.2011.05.049</u>.
- Tremblay S, Rogasch NC, Premoli I, Blumberger DM, Casarotto S, Chen R, Di Lazzaro V, Farzan F, Ferrarelli F, Fitzgerald PB, Hui J, Ilmoniemi RJ, Kimiskidis VK, Kugiumtzis D, Lioumis P, Pascual-Leone A, Pellicciari MC, Rajji T, Thut G, Zomorrodi R, Ziemann U, Daskalakis ZJ. Clinical utility and prospective of TMS-EEG. Clin Neurophysiol 2019;130(5):802–44. <u>https://doi.org/10.1016/</u> i.clinph.2019.01.001.
- Tremblay S, Tuominen L, Zayed V, Pascual-Leone A, Joutsa J. The study of noninvasive brain stimulation using molecular brain imaging: A systematic review. Neuroimage 2020;219:117023. <u>https://doi.org/10.1016/j.</u> neuroimage.2020.117023.
- Trippe J, Mix A, Aydin-Abidin S, Funke K, Benali A. Theta burst and conventional low-frequency rTMS differentially affect GABAergic neurotransmission in the rat cortex. Exp Brain Res 2009;199(3-4):411–21. <u>https://doi.org/10.1007/ s00221-009-1961-8</u>.
- Trojak B, Meille V, Gelinier J-CC-, Bonin B. Does the Intensity of Transcranial Magnetic Stimulation Need to be Adjusted to Scalp-Cortex Distance? J Neuropsychiatry Clin Neurosci 2012;24:E13.

#### M. Desforges, I. Hadas, B. Mihov et al.

- Vernet M, Bashir S, Yoo WK, Perez JM, Najib U, Pascual-Leone A. Insights on the neural basis of motor plasticity induced by theta burst stimulation from TMS-EEG. Eur J Neurosci 2013;37:598–606. <u>https://doi.org/10.1038/iid.2014.371</u>.
- Voineskos D, Blumberger DM, Zomorrodi R, Rogasch NC, Farzan F, Foussias G, Rajji TK, Daskalakis ZJ. Altered Transcranial Magnetic Stimulation-Electroencephalographic Markers of Inhibition and Excitation in the Dorsolateral Prefrontal Cortex in Major Depressive Disorder. Biol Psychiatry 2019;85(6):477–86. <u>https://doi.org/10.1016/j.biopsych.2018.09.032</u>.
- Volz LJ, Benali A, Mix A, Neubacher U, Funke K. Dose-dependence of changes in cortical protein expression induced with repeated transcranial magnetic thetaburst stimulation in the rat. Brain Stimul 2013;6(4):598–606. <u>https://doi.org/ 10.1016/j.brs.2013.01.008</u>.
- Williams NR, Sudheimer KD, Bentzley BS, Pannu J, Stimpson KH, Duvio D, et al. High-dose spaced theta-burst TMS as a rapid-acting antidepressant in highly refractory depression. Brain 2018;141:e18. https://doi.org/10.1093/brain/ awx379.
- Woźniak-Kwaśniewska A, Szekely D, Aussedat P, Bougerol T, David O. Changes of oscillatory brain activity induced by repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in healthy subjects. Neuroimage 2014;88:91–9. <u>https://doi.org/10.1016/j.neuroimage.2013.11.029</u>.

- Xing H, Xu S, Xie X, Wang Y, Lu C, Han X. Levetiracetam induction of theta frequency oscillations in rodent hippocampus in vitro. Can J Physiol Pharmacol 2020. https://doi.org/10.1139/cjpp-2019-0727.
- Woźniak-Kwaśniewska A, Szekely D, Harquel S, Bougerol T, David O. Resting electroencephalographic correlates of the clinical response to repetitive transcranial magnetic stimulation: A preliminary comparison between unipolar and bipolar depression. J Affect Disord 2015;183:15–21. <u>https://doi. org/10.1016/i.iad.2015.04.029</u>.
- Zavorotnyy M, Zöllner R, Rekate H, Dietsche P, Bopp M, Sommer J, Meller T, Krug A, Nenadić I. Intermittent theta-burst stimulation moderates interaction between increment of N-Acetyl-Aspartate in anterior cingulate and improvement of unipolar depression. Brain Stimul 2020;13(4):943–52. <u>https://doi.org/10.1016/ i.brs.2020.03.015</u>.
- Ziemann U, Siebner HR. Inter-subject and intersession variability of plasticity induction by non-invasive brain stimulation: Boon or bane? Brain Stimul 2015;8(3):662–3. <u>https://doi.org/10.1016/j.brs.2015.01.409</u>.
- Zmeykina E, Mittner M, Paulus W, Turi Z. Weak rTMS-induced electric fields produce neural entrainment in humans. Sci Rep 2020;10(1). <u>https://doi.org/ 10.1038/s41598-020-68687-8</u>.